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PERSPECTIVE

COVID-19 and toxicity from potential treatments: Panacea or poison

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Abstract

Since December 2019, coronavirus disease (COVID-19) has been increasingly spreading from its origin in Wuhan, China to many countries around the world eventuating in morbidity and mortality affecting millions of people. This pandemic has proven to be a challenge given that there is no immediate cure, no vaccine is currently available and medications or treatments being used are still undergoing clinical trials. There have already been examples of self-medication and overdose. Clearly, there is a need to further define the efficacy of treatments used in the management of COVID-19. This evidence needs to be backed by large randomised-controlled clinical trials. In the meantime, there will no doubt be further off-label use of these medications by patients and practitioners and possibly related toxicity.

Key words: *coronavirus, COVID, overdose, toxicology.*

Since December 2019, coronavirus disease (COVID-19) has been increasingly spreading from its origin in Wuhan, China to many countries around the world eventuating in morbidity and mortality affecting millions of people.[1] This pandemic has proven to be a challenge given that there is no immediate cure, no vaccine is currently available and medications or treatments being used are still undergoing clinical trials.

Despite many medications being trialled for use in COVID-19 management, there seem to be some misinformed opinions on the efficacy of these. A prime example is the President of the United States promotion of hydroxychloroquine. One of his tweets dated 22 March 2020 (Twitter hashtag @realdonaldtrump), labelled hydroxychloroquine and azithromycin as 'one of the biggest game-changers in the history of medicine'. One of the repercussions of promotion of medications/treatments prior to the results of large robust clinical trials being available is that people may start to self-medicate and potentially overdose. This is exemplified by the report of an Arizona man dying having ingested chloroquine, which he had been using to prevent parasite infection in fish.[2] In addition, his wife had ended up in critical care. Although this was not the prescribed tablet form of chloroquine, it does highlight the dangers of self-medication regardless which can also affect others.

As emergency doctors, we need to be able to tease out the disease process of COVID-19 from potential side effects of trial medications or overdose of these. While not an extensive list of the numerous therapies being tested, some of the most notable or ones that have garnered media attention will be discussed here.

Chloroquine/ hydroxychloroquine

Chloroquine and hydroxychloroquine have been used as antimalarials and for rheumatic disease treatment for many years with much success. They have been used in the setting of COVID-19 because they inhibit endosomal acidification required for virus-host cell fusion. In overdose, these drugs can cause hypotension, hypokalemia, QRS and QT prolongation, atrioventricular block, arrhythmias and coma. Chloroquine and hydroxychloroquine also have a narrow therapeutic index which can cause significant toxicity in children accidently taking a single adult dose.[3]

There have been conflicting studies regarding the use of hydroxychloroquine. A small (n = 42), non-randomised open label trial showed decreased viral load in patients receiving hydroxychloroquine (600 mg daily for 10 days) and azithromycin.[4] However, there was no analysis of clinical benefit and only short-term follow up. Another study of 181 patients with COVID-19 pneumonia (84 receiving hydroxychloroquine within 48 h of admission and 97 that did not), showed no difference in ICU transfer or mortality within 7 days.[5] While neither of these studies are conclusive, there are numerous larger controlled trials set to study this further.

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Azithromycin

Azithromycin is a macrolide antibiotic which has been used in conjunction with hydroxychloroquine for the management of COVID. In one Brazilian double blind, randomised, parallel trial examining two different doses of chloroquine in addition to ceftriaxone or azithromycin patient, recruitment was halted prematurely. The higher dose chloroquine regimen (650 mg BD for 10 days) resulted in 18.9% of patients developing a QTc >500 ms and 2.7% with ventricular tachycardia with a trend towards higher lethality compared to the lower dosage (450 mg BD for 5 days).[6] This might be explained by both azithromycin and chloroquine both known to prolong the QT interval. However, the ventricular tachycardia episodes were not due to Torsades des Pointes, which patients are at increased risk with prolonged QT. In addition, complications of COVID-19 such as myocarditis might further contribute to the clinical picture.

Nucleoside analogues (e.g. remdesivir)

Nucleoside analogues inhibit viral RNA polymerase which is a key in viral replication. Remdesivir has been used previously to treat Ebola and recently has been prescribed to a small cohort study of COVID-19 patients.[7] In the present study, 53 patients who received remdesivir were analysed and 36 of 53 (58%) showed clinical improvement. However, the study was criticised by not having a control group and larger RCTs are pending. Side effects noted included elevated aminotransferase enzymes, diarrhoea, rash and renal impairment.

Viral protease inhibitors (e.g. lopinavir/ritonavir)

The lopinavir/ritonavir combination has shown *in vitro* activity against severe acute respiratory syndrome (SARS) previously. It has been used for the treatment of human immunodeficiency virus. They are potent inhibitors of CYP3A4, CYP2D6 enzymes and P-glycoprotein and therefore may interact with other medications. Side effects include gastrointestinal upset and liver injury. In the setting of overdose, lactic acidosis renal injury, central nervous system depression, seizures and cardiac arrhythmias have been reported previously.[8]

Colchicine

Colchicine is used commonly for the management of gout and other conditions. Colchicine inhibits microtubule polymerisation by binding to tubulin and inhibits cell mitosis among its other anti-inflammatory actions. In overdose, this can lead to gastrointestinal symptoms, fluid loss, cardiovascular collapse and arrhythmias, bone marrow and multi-organ failure. Treatment of toxicity includes decontamination with active charcoal but overall remains largely supportive.

Ivermectin

Ivermectin is an anti-parasitic agent used to treat conditions such as pinworm, threadworm, whipworm infection, head lice and lymphatic filariasis. Recently, there has been intense media interest in a study showing *in vitro* inhibition of COVID-19 with ivermectin.[9] So much so the authors have released a statement that this medication has not been studied in humans in the setting of COVID-19 infection. In overdose, ivermectin can lead to gastrointestinal symptoms, hypersalivation, drowsiness, muscle weakness, tachycardia, hypotension, ataxia, agitation, rhabdomyolysis and coma.

Checkpoint inhibitors (e.g. tocilizumab)

The cytokine storm as a result of COVID-19 can result in severe multi-organ dysfunction and death. Interleukin-6 (IL-6) plays a key role in cytokine release syndrome. Tocilizumab is a recombinant monoclonal antibody used against IL-6 and has previously been used to treated rheumatoid arthritis. Side effects with therapeutic use include headache, elevated liver enzymes, myelosuppression, haemorrhage and pancreatitis and convulsions.

Thalidomide

Thalidomide has been used to treat a number of cancers including multiple myeloma. Infamously, it was promoted for use in anxiety, insomnia and morning sickness. In the 1960s, it was removed from the market because of its teratogenic effects. Acute thalidomide overdose can result in drowsiness, hypotension and coma. A clinical trial has been registered for its use.[10]

Clearly there is a need to further define the efficacy of treatments used in the management of COVID-19. This evidence needs to be backed by large randomised-controlled clinical trials and undergo rigorous peer review before publication. In the meantime, there will no doubt be further off-label use of these medications by patients and practitioners and possibly related toxicity. One of the principles in medical ethics is 'primum non nocere' or 'first do no harm'. During the COVID pandemic, we must continue to be advocates of high-quality evidence-based medicine to inform management of our patients and be aware of the toxicity that some of the treatments may cause.

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Competing interests

None declared.

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